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Pharmacokinetics of Oral Methadone in the Treatment of Neonatal Abstinence Syndrome: A Pilot Study

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Abstract

Objective—To characterize the population pharmacokinetic (PK) of oral methadone in neonates requiring pharmacologic treatment of neonatal abstinence syndrome (NAS) and to develop a PK model towards an evidence-based treatment protocol.

Study design—Based on a methadone dosing protocol, serum concentrations of methadone and its metabolites were assessed via high performance liquid chromatography-tandem mass spectrometry from dried blood spots. Population PK analysis was performed to determine the volume of distribution and clearance of oral methadone. Methadone plasma concentration-time profiles were simulated from the deduced PK model to optimize the dosing regimen.

Results—There was substantial inter-individual variability in methadone concentrations. Blood concentrations of methadone were best described by a one-compartment model with first-order absorption. The population mean estimates (coefficient of variation percentage) for oral clearance and volume of distribution were 8.94 (103%) L/h/70 kg and 177 (133%) L/70 kg, respectively. Optimized dosing strategies were developed based on the simulated PK profiles. We suggest a starting dose of 0.1 mg/kg per dose every 6 hours for most patients requiring pharmacologic treatment of NAS followed by an expedited weaning phase.

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The authors declare no conflicts of interest.

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Conclusions—The proposed dosing regimen may reduce the cumulative dose of opioid and shorten the length of hospitalization. Future studies should aim to validate the simulated dosing schemes with clinical data and expand our understanding of the between-patient PK variability.

Trial registration—ClinicalTrials.gov: NCT01754324

Keywords

Infant; Methadone; NAS; Neonatal Abstinence Syndrome; Neonate; NONMEM; Opioid; Opiate; Pharmacokinetic; Pregnancy; Withdrawal

Neonatal abstinence syndrome (NAS) is a condition unique to the newborn period that results from the abrupt cessation of chronic intrauterine drug exposure following birth. NAS severe enough to require pharmacologic intervention most frequently occurs following opioid exposure. Chronic *in utero* exposure to opioids is a public health burden due to its increasing prevalence, frequent need for pharmacotherapy to mitigate signs of withdrawal, prolonged hospitalization and excessive cost^{1–3}. Opioid use in the United States is highly prevalent^{4,5} with a 5-fold increase during pregnancy over the last decade, affecting 5.6 per 1000 births^{6,7}. Much of this increase may be attributed to ubiquitous narcotic prescription for pain relief generally and in pregnancy^{8–10}. The incidence of NAS has tripled from 1.20 to 3.39 per 1000 hospital births and is increasing in its geographic distribution^{7, 11}. In a recent prospective study, as many as 57% of infants born to mothers receiving opioid maintenance therapy required pharmacologic treatment, though the presence of withdrawal symptoms has been reported to be as high as 94%^{1,12}.

Opioid replacement is the standard treatment for severe opioid withdrawal in neonates. Many pharmacologic treatment protocols using a variety of drugs have been proposed for the treatment of NAS^{13,14}. No standardized, universally accepted treatment exists, though the agents commonly used in the majority of protocols involve methadone (20%) or other opioids (63%)¹⁵. Most infants with NAS respond well to therapy with oral methadone. Strikingly, there are minimal pharmacokinetic (PK) data available to guide pharmacologic treatment strategies with oral methadone despite several studies suggesting that it may be an equivalent, if not superior alternative, to morphine in the treatment of NAS^{16–18}. For this reason, the Best Pharmaceuticals for Children Act (BPCA) of the US Food and Drug Administration includes methadone on its list of priority drugs requiring additional dosing data¹⁹. The PK of oral methadone has been described for adults receiving methadone for opioid dependence and the PK of intravenous methadone used for pain control has been reported for adolescents and neonates^{20–22}. We aimed to assess the PK of methadone after oral administration in infants progressing through a standardized step-wise methadone tapering protocol. The use of a formal treatment protocol has been shown to decrease hospital length of stay¹⁶. However, understanding the PK of oral methadone is required for designing evidence-based treatment protocols.

METHODS

Institutional review boards at Cincinnati Children’s Hospital Medical Center, University of Cincinnati Medical Center and Mercy Hospital Anderson (Cincinnati, Ohio) all approved

the study protocol. Informed consent was obtained from the legal guardians of all the subjects enrolled. Each participant had a history of chronic intrauterine exposure to opioids and required pharmacologic treatment with oral methadone to mitigate signs of NAS. Acutely ill neonates, infants with congenital abnormalities or medical illnesses necessitating opioid treatment for conditions other than NAS, and infants who were wards of the state were excluded.

The decision to treat infants exposed to opioids in utero rested with the medical team and was predicated upon the severity of withdrawal symptoms assessed using the Finnegan Neonatal Abstinence Scoring Tool (Finnegan) in all recruitment sites. Administrators of the Finnegan were educated using the D'Apollito Reliability Training (including an interactive DVD and proctored scoring) ^{16,23}. In general, hospital protocols dictated that Finnegan scores be assigned every 3–4 hours starting within 24 hours of age for all infants exposed to opioids. Neonates with scores ≥ 8 were transferred to the neonatal intensive care unit for closer observation. Particular effort was exerted to minimize external stimulation including the use of dimmed ambient lighting and swaddling per unit protocol. Pharmacologic therapy with oral methadone was initiated in neonates having three consecutive scores ≥ 8 or two consecutive scores ≥ 12 in a 24-hour period. Administrators of Finnegan scores were not masked to prior scores or treatment.

The dosing guidelines for medications used were the same at all participating institutions and for all patients enrolled in the study (Table I). In brief, all infants were started on oral methadone treatment at 0.05 mg/kg/dose every 6 hours. Infants who responded with reduced withdrawal scores over the first 24 hours were weaned to 0.04 mg/kg/dose every 6 hours (Step 2) and continued with the step-wise dosage decreases outlined (Scheme 1). The clinical team was at liberty to wean the methadone dose more quickly than scheduled per protocol if there was concern for somnolence or consistently low Finnegan scores. This occurred twice and was done after study-related blood samples were obtained. In contrast, when the Finnegan scores failed to abate over the first 24 hours of treatment, the methadone dose was increased to 0.1 mg/kg/dose every 6 hours (Step 1A) and was subsequently weaned per protocol after stabilization of withdrawal scores (Scheme 2). Infants who failed to tolerate weaning the methadone dose every 24 to 48 hours or who backslid on dosing to recapture recurrent symptoms were started on phenobarbital. Subjects receiving phenobarbital were given an oral loading dose of 10 mg/kg followed by a daily dose of 5 mg/kg. The timing of adjunctive therapy with phenobarbital initiation was at the discretion of the clinical team. For the purposes of this study, the time to capture symptoms was documented. The time to capture was defined as the time required to attain two consecutive decreases in Finnegan scores below 12 (if therapy was initiated for 2 consecutive scores ≥ 12) or two consecutive decreases below 8 (if therapy was initiated for 3 consecutive scores ≥ 8) after initiation of pharmacotherapy. Blood specimens for PK studies (clearance and volume of distribution) were obtained within 72 hours of commencement of oral methadone regardless of the dosing scheme.

We used a D-optimal sparse blood sampling design with nonparametric population modeling to allow for PK variable estimation while minimizing the need for frequent blood sampling. Three or four blood specimens were collected from each patient. The first 3 specimens

involved timed collections related to a single methadone dosing (just before a dose of methadone, 1–2 hours after that dose and just prior to the next dose). Most families consented to an optional fourth blood sample obtained just prior to a methadone dose after the participant failed to respond to treatment as anticipated. Concentrations of methadone and its biologically inactive metabolites in dried blood spots on Guthrie cards were determined using a high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay at the University of Colorado, Aurora, CO, as previously published^{24–26}. The lower limit of quantitation was 0.25 ng/mL for methadone and 0.1 ng/mL for 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline (EMDP).

Outcome Measures

The primary PK outcome measure was clearance of oral methadone from blood. Large between-subject variability in serum methadone concentrations has been reported in PK studies of oral methadone in adults, a finding that is presumed to be valid in infants^{27,28}. In order to better understand the scope of this variability in neonates and identify the sample size needed to power a full characterization study of methadone in the neonate, a goal enrollment of 20 patients was selected for this pilot study. This was sufficient to achieve precision criteria recommendations for pediatric PK studies, giving 95% confidence intervals for mean estimates of methadone clearance and volume of distribution with at least 80% power²⁹. Secondary outcome measures included length of hospitalization, need for adjunctive pharmacologic treatment, thirty day hospital readmission rate, sustained clinical resolution of symptoms after discharge from the hospital as assessed by 2 week follow-up phone call and associations between the serum concentrations of methadone and its metabolites (EDDP and EMDP) and clinical response to a standardized tapering protocol.

Pharmacokinetic Analyses and Simulation

Population PK analysis was performed by non-linear mixed effects modeling with NONMEM software (version 7.2.0, ICON, Ellicott City, MD). NONMEM uses a combination of “fixed” effects (like volume of distribution and clearance) and “random” effects (like random error and differences between individuals and observations) to describe PK variables for a population. During model development, the data were assessed for fit with one- and two-compartment models. The models were then evaluated for goodness of fit and stability. Additional details and rationale of the model development including adjustment for age and maturation are described in the Appendix (available at www.jpeds.com). The final one-compartment PK model was used to simulate one thousand methadone blood concentration-time profiles in order to design a new dosing strategy. An assumed body weight of 3 kg was used as a typical value and population means for the area under the curve (AUC) at 24, 48 and 72 hours of methadone treatment were generated for dosing Schemes 1 and 2 (Table I). The AUC was used to assess the extent of drug exposure with respect to time in this cohort of patients. A target AUC for the simulated dosing regimens was determined *post-hoc* by analyzing the AUC population means and medians and correlating them with Finnegan scores (a marker for clinical response) to describe overall drug effect. New simulated dosing regimens were devised to achieve the target AUC in the first 24–48 hours of therapy.

Statistical Analyses of Secondary Outcomes

We examined relationships among patient demographics, length of stay, and pharmacologic variables. Spearman rank correlation was used to test the relationship between infant cord blood methadone concentrations and length of hospital stay. Wilcoxon rank sum test was used to test for differences in infant blood methadone concentrations by need for higher initial dose (Scheme 2) or inability to progress through the protocol. All statistical analyses were performed with SAS software (version 9.3, SAS institute, Cary, NC).

RESULTS

Of the 64 neonates exposed to opioids December 2012 to October 2013, 34 were excluded (26 infants did not require pharmacologic treatment, 2 were preterm, 3 were wards of the state, 3 were treated with buprenorphine) and 2 infants were missed. Eight of the remaining 28 patients declined participation in the study. As a result, twenty term neonates, comprising 71% of eligible subjects, were enrolled in the study (Table II; available at www.jpeds.com).

Population PK Analysis

Seventy-one blood specimens were obtained from 20 patients and included 11 optional fourth blood samples. The 11 conditional specimens were collected after either therapy escalation to Scheme 2 (n=6) or after failure to tolerate weans (n=5). Specimens obtained after failure to tolerate weans were not included in the final PK model because they were confounded by increased body weight >25% in that subset of patients. Therefore, only serial PK data generated within 4 days of treatment initiation were used for the development of the final population PK model. The large fluctuation in body weight may be attributed to catch-up growth after growth restriction in utero and hyperphagia secondary to withdrawal. Patients on an *ad lib* feeding schedule would often consume 180–220 ml/kg/day. At the time of blood sampling, no patients were receiving phenobarbital. Concentrations of methadone were highly variable, ranging from 1.47 ng/mL to 198 ng/mL (Figure 1). Of note, the three specimens ranging between 174 and 198 ng/mL were obtained from the same subject. Methadone metabolite concentration profiles mirrored the inter-individual variability noted with the parent drug (Figure 2; available at www.jpeds.com).

The concentration profile of methadone was best described with a one-compartment model with first order absorption and lag-time. The diagnostic plots affirm that the PK profiles are well captured in the final PK model (Figure 3; available at www.jpeds.com). Estimated PK variables are summarized in Table III as well as the median values and 95% confidence intervals from the nonparametric percentile bootstrap analysis, which indicate the stability of the model. The population mean values (coefficient of variation percentage) for clearance and volume of distribution were 8.94 (103%) L/h/70 kg and 177 (133%) L/70 kg, respectively. A PK analysis excluding blood concentrations greater than the 95th percentile was also performed; however, clearance estimates were not greatly affected (9.33 vs 8.94 L/h/70 kg) though between-subject variability decreased (87.6% vs 103%). Therefore, all data were included in the reported estimates.

PK Simulation for the Dosing Regimen Design

On the basis of the observed population PK and clinical response to treatment, we endeavored to model new dosing regimens (Figure 4). Infants treated with our current standard dosing protocol (Scheme 1, n = 12) had Finnegan scores that normalized within the first 48 hours, whereas it took patients treated with the higher dose schedule (Scheme 2, n = 8) approximately 72 hours for scores to stabilize. Therefore, we postulated a dose exposure between the mean and median AUC after 48 hours for Scheme 1 patients (1261 and 816 ng•h/mL, respectively) and 72 hours for Scheme 2 patients (3375 and 2274 ng•h/mL, respectively) to be a reasonable target for the mitigation of withdrawal signs. We aimed to achieve the target AUC expeditiously using two clinically convenient dosing regimens while minimizing the risk of potential adverse effects such as respiratory depression. One thousand iterations were used to fully predict the distribution of the simulated methadone concentration profiles using the final PK model and the newly-proposed dosing regimens (Figures 4)³⁰. From this simulation, the AUC at 24 hours for the new Scheme 1 is 985 ± 1020 ng•h/mL and the AUC at 48 hours for the new Scheme 2 is 3073 ± 2979 ng•h/mL, suggesting that the time to attain target blood concentrations could be decreased by approximately 24 hours.

Secondary Outcomes

Clinical outcomes are summarized in Table IV (available at www.jpeds.com). We obtained umbilical cord blood for 9 of the 10 infants delivered to mothers on methadone at the time of delivery but the methadone concentrations (63.2 ± 55.4 ng/mL) were not significantly correlated with length of stay (Spearman $\rho = 0.45$, $p = 0.22$). The median length of hospitalization for all patients enrolled was 18.5 days (IQR: 16, 30). Ten participants (50%) failed to wean on at least one step of the protocol, 8 (40%) required the higher dosing protocol (Scheme 2) and 4 (20%) experienced both. Infants that required the higher dosing schedule because they could not progress through the weaning protocol had higher serum methadone concentrations at 24 hours of treatment, though these differences were not statistically significant (45.3 ± 33.9 ng/mL vs 41.2 ± 61.7 ng/mL, $p = 0.86$). Eleven (55%) of enrolled subjects received adjunctive pharmacologic treatment (phenobarbital) but none required hospital readmission within thirty days of discharge. Eleven participants responded to follow-up phone calls to assess sustained resolution of withdrawal symptoms. The most common residual symptoms were jitteriness (8/11), fussiness (6/11) and increased muscle tone (4/11). No complaints of seizure, diarrhea or feeding difficulty were reported.

DISCUSSION

Our study assessed the PK of oral methadone in neonates. The population PK analysis suggests that clearance and volume of distribution normalized by allometrically scaled body weights are comparable with adult values and are congruent with recently published data on intravenous methadone^{20–22,31}. Ward et al reported the clearance of intravenous methadone to be 9.1 L/h/70 kg with a volume of distribution of 581 L/70 kg in neonates, and Stemland et al demonstrated a clearance of 9.33 L/h/70 kg and volume of distribution of 570 L/70 kg in adolescents^{21,22}. By way of comparison, Foster et al reported the clearance and volume of distribution for oral methadone in adults with opioid dependence to be 8.5 L/h/70 kg and

433 L/70 kg respectively²⁰. Minor differences in the observed volume of distribution as compared with studies involving intravenous methadone are likely due to differences in bioavailability and the use of a one-compartment model as opposed to the two- or three-compartment models used in other published reports.

Strengths of our study include the use of minimally invasive techniques to obtain specimens (dried blood spot sampling) and reducing disruption to patient care (sparse sampling design). This study demonstrates the feasibility of obtaining methadone concentrations from dried blood spots in the clinical setting. This modality requires much less blood from the patient (3–4 drops), does not necessitate venipuncture that is often required for traditional pharmacologic studies and appeared to be an important consideration for parents who were concerned about discomfort and phlebotomy blood loss. Additionally, blood sampling may be synchronized with clinical care in a sparse sampling design. We feel this was very important to a population of neonates who are often hypersensitive to interventions and stimulations. The high congruence with other neonatal data for intravenous methadone also strengthens confidence in the population PK findings. Subsequently, the new simulation-derived treatment protocols have been adopted by most treatment centers in the Cincinnati area, including all of the study sites.

Potential benefits of implementing the newly-proposed dosing schemes include a shortened length of time to progress through the treatment protocol by three days, decreased cumulative drug exposure by up to 10% and reduction in total drug doses by up to 48% which minimizes the chance for dosing error, lessened labor (staff time) and potentially lowered cost of care (Figure 4). An argument could be made that the high number of infants requiring management with phenobarbital (55%) might suggest the need to be more conservative with weaning protocols. However, this is likely a function of the small sample size, as it differs from its baseline use of phenobarbital in the participating institutions (27%).

In the proposed PK-based dosing protocols, our model predicts that the AUC targets will be achieved in the first 24 or 48 hours as opposed to 48 or 72 hours needed for the old treatment tapers. Down titration for both dosing schemes involve moderate decreases in dose every 24 hours based on signs or withdrawal scores until a dose of 0.01 mg/kg every 24 hours is attained, after which the medication is discontinued (Figure 4). The proposed protocol changes would increase early dose exposure and the peak methadone concentration, thereby decreasing the frequency at which treatment escalation is needed. We suggest that Scheme 2 be considered in the initial treatment of infants with scores ≥ 12 , because the mean Finnegan score for infants requiring the dose escalation strategy during the 24 hours prior to treatment was 11 ± 1.6 .

Somnolence and respiratory depression are very rare in monitored settings, but with higher initial dosing in the new treatment schemes, it would be prudent for practitioners wishing to implement the protocol to avoid extension to an outpatient treatment setting until additional safety studies are available.

With the evidence-based PK model for oral methadone proposed in this study, future investigations may focus on outcomes associated with the proposed treatment protocols, addressing the large inter-individual variability in methadone blood concentrations with more robust sampling and comparison studies with other first-line therapies such as morphine. As bedside point-of-care LC-MS/MS technology is developed and validated, future studies could also investigate the feasibility and utility of obtaining real-time drug concentrations that, in combination with model-based Bayesian interpretation, can be used to implement personalized treatment strategies³².

Study limitations include the small sample size inherent in a pilot study like ours. Also, there is no validated, completely objective scoring system to assess clinical response to pharmacologic therapy in NAS; however, we endeavored to minimize inter-observer variability by ensuring that all staff ascribing Finnegan scores underwent training in the scoring system. Additionally, the large inter-individual variability in methadone concentrations limits the predictability of individual response to our newly-proposed methadone regimens that are based on population estimates. Though the dosing strategies offer an improved, evidence-based approach to the pharmacologic treatment of NAS with oral methadone, a larger study is needed to acquire further PK data and formulate more individualized dosing strategies. Also, a one-compartment model for oral methadone best described the PK profiles in this study, in contrast to population PK studies of intravenous methadone that reported two- and three-compartment models^{22,31}. The difference between sparse and frequent sampling study designs may explain this discrepancy. Only 3 or 4 blood specimens were analyzed per participant in this study, in contrast to the 10 plasma concentrations that were often obtained per patient in the cited studies, which enabled the authors to describe early methadone distribution to multiple compartments and the ability to utilize more complex models. However, our simpler one-compartment model adequately characterized the methadone concentration profiles and is sufficient to predict methadone concentrations and exposure (AUC) in neonates.

Based on data from this pilot study, we propose modifications to the current treatment protocol using oral methadone in order to optimize care and decrease hospital length of stay. Due to substantial inter-individual PK variability and clinical response, a larger study is warranted to address gaps in PK and pharmacodynamic knowledge, to better characterize demographic factors that are predictive of severity of withdrawal symptoms, establish pharmacogenetic data, develop biomarkers for therapeutic response to oral methadone and advance the development of bedside personalized dosing strategies.

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Abbreviations

AUC	Area Under the Curve
EDDP	2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine
EMDP	2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline
NICU	Newborn Intensive Care Unit
NAS	Neonatal Abstinence Syndrome
PK	Pharmacokinetic

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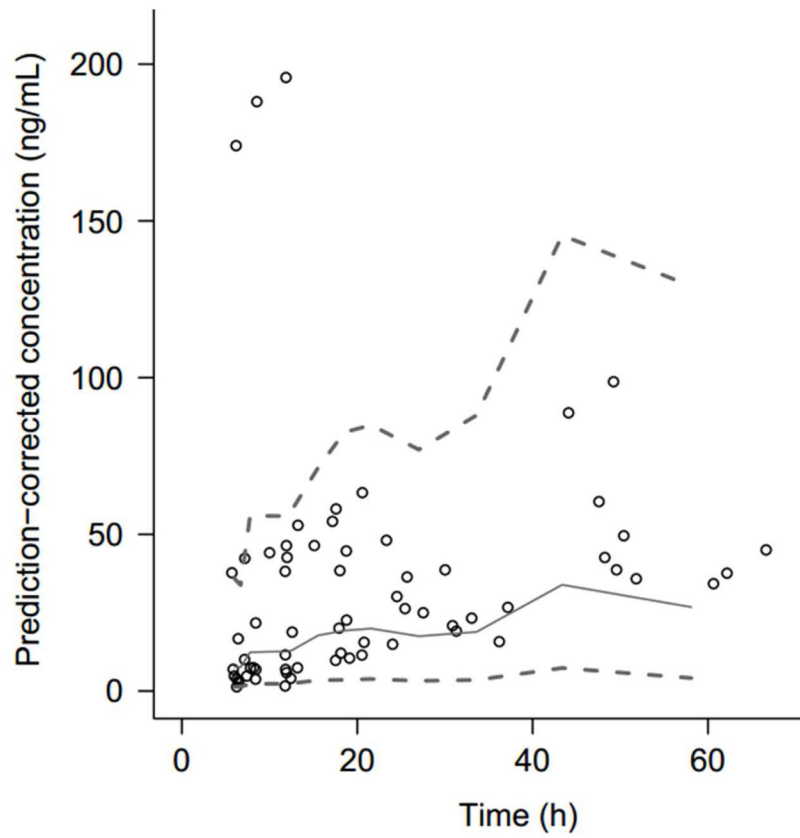


Figure 1. Observed methadone blood concentrations versus time. Solid line represents the population mean. Dashed lines represent the 5th and 95th percentiles.

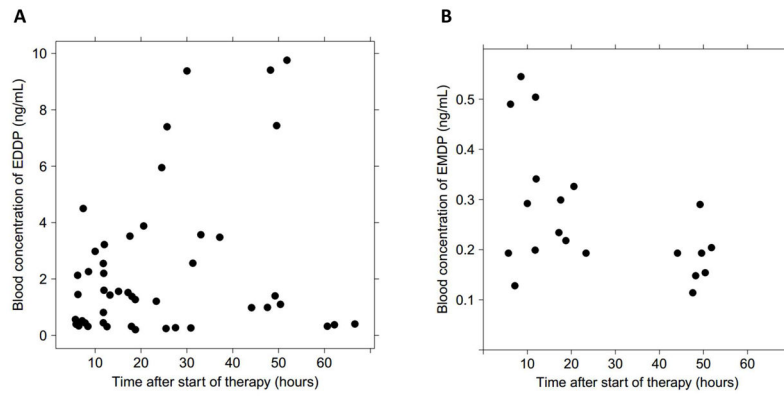


Figure 2. Observed blood concentrations of methadone metabolites versus time. (A) Blood EDDP concentration vs. time. (B) Blood EMDP concentration vs. time. Blood concentrations were below the limit of quantitation for EDDP in 6 patients and for EMDP in 14 patients.

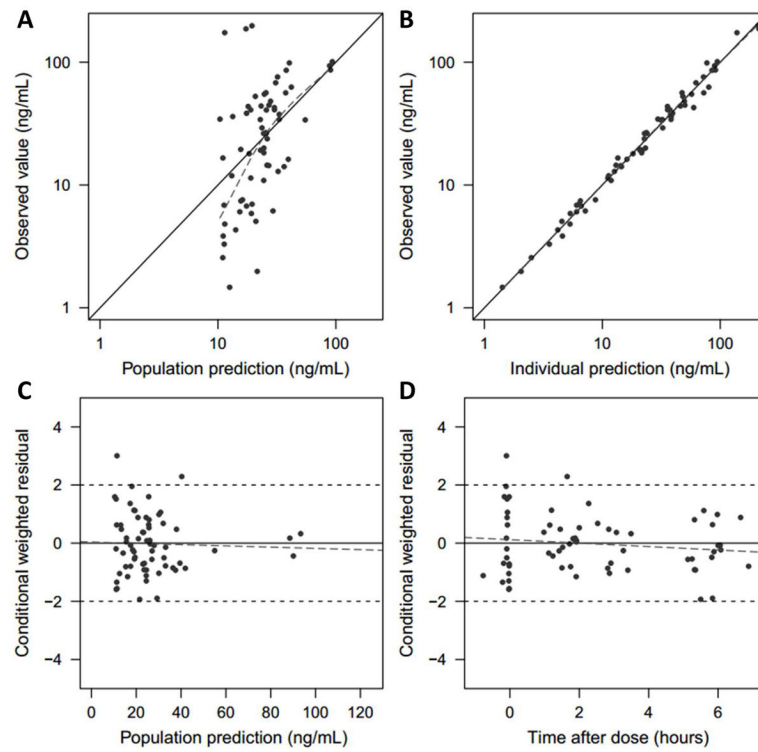


Figure 3. Goodness-of-fit plots for the final model. (A) Observed value vs. population predicted value, (B) Observed value vs. individual predicted value, (C) Conditional weighted residuals (CWRES) vs. population predicted value and (D) CWRES vs. time after the dose.

Figure 4A

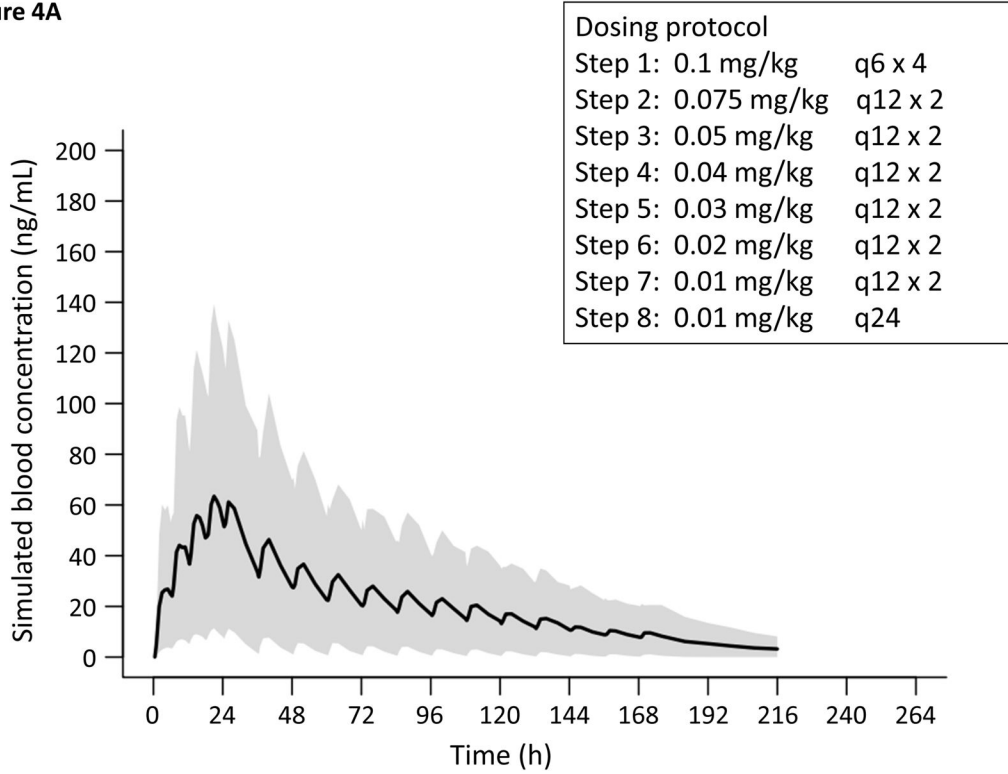


Figure 4B

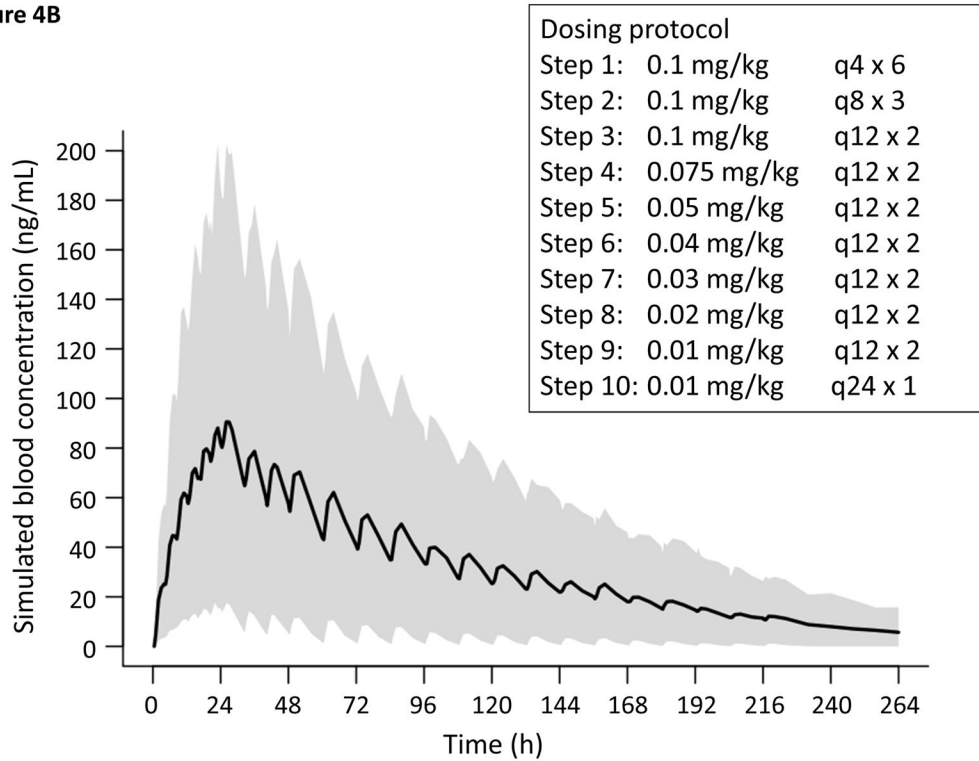


Figure 4.

Simulated PK of oral methadone for a term 3-kilogram infant based on the final PK model. Solid line and gray shaded area represents the predicted mean and range (10th–90th percentile), respectively of methadone plasma concentrations from 1000 simulations. Concentration vs. time for new tapering in A, Scheme 1 and B, Scheme 2.

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Table 1

Oral methadone dosing scheme

Taper Step	Dose (mg/kg)	Frequency	Number of Doses
1	0.05	q6	x4
1A*	0.1	q6	x4
1B*	0.075	q6	x4
1C*	0.05	q6	x4
2	0.04	q6	x4
3	0.03	q6	x4
4	0.02	q6	x4
5	0.02	q8	x3
6	0.02	q12	x4
7	0.01	q12	x4
8	0.01	q24	x2

* Scheme 2: Used only for infants that are recalcitrant to Scheme 1 (weaning directly from Step 1 to Step 2).

Table 2

Characteristics of study participants (N=20)

Male, N (%)	9 (45)
Non-hispanic White, N (%)	20 (100)
Gestational age in weeks, Median [IQR]	38 [37.4, 39.5]
Birth weight in kg, Median [IQR]	3.0 [2.6, 3.2]
Mode of Delivery	N (%)
Vaginal	16 (80)
Cesarean	4 (20)
Drug of exposure	N (%)
Methadone	10 (50)
Heroin	7 (35)
Buprenorphine	6 (30)
Other opioids (Oxycodone, Hydrocodone)	7 (35)
Benzodiazepines	4 (20)
Marijuana	4 (20)
Cocaine	2 (10)
Tobacco	18 (90)
Multiple opioids, N (%)	12 (60)
Opioid plus other substances of abuse, N (%)	8 (40)
Age in hours at initiation of methadone, Median [IQR]	32.2 [27.2, 42.7]
Finnegan scores, Median [IQR]	13.0 [11.0, 14.2]
Time to capture in days, Median [IQR]	1.4 [0.90, 1.7]
Breastfeeding initiated, N (%)	4 (20)
Discharge weight in kg, Median [IQR]	3.4 [3.0, 3.7]

Abbreviations: N (number of patients), IQR (interquartile range)

Table 3

Variable estimates for the final population PK model

	Estimates	%RSE	Bootstrap analysis (n=1000)	
			Median	95% CI
CL/F in L/h/70 kg	8.94	19	8.37	4.73 – 12.8
CL/F in L/h/kg	0.37			
Vd/F in L/70 kg	177	40	174	37.2 – 428
Vd/F in L/kg	2.53			
Ka in h ⁻¹	0.334	24	0.346	0.140 – 0.659
Lag time in h	0.827	33	0.837	0.0956 – 1.14
Interindividual variability, CV%				
IIV for CL/F	103	14	99.9	50.5 – 132
IIV for Vd/F	133	19	130	79.1 – 161
Residual variability, CV%				
Proportional error	15.7	10	15.6	12.4 – 18.1
Simulated AUC for Scheme 1	Median	IQR		
AUC ₀₋₂₄ h in ng-h/mL	316	166–584		
AUC ₀₋₄₈ h in ng-h/mL	816	459–1557		
AUC ₀₋₇₂ h in ng-h/mL	1378	768–1583		
Simulated AUC for Scheme 2				
AUC ₀₋₂₄ h in ng-h/mL	333	183–629		
AUC ₀₋₄₈ h in ng-h/mL	1257	697–2287		
AUC ₀₋₇₂ h in ng-h/mL	2274	1238–4253		

Abbreviations: CL (clearance), CV (coefficient of variation), F (bioavailability), IIV (inter-individual variability), ka (absorption rate constant), Vd (volume of distribution), RSE (relative standard error), CI (confidence interval), AUC (area under the concentration-time curve), IQR (Interquartile range).

Table 4

Clinical Outcomes

	Value	Variation or Percent
Median length of hospitalization in days	18.5	IQR [16, 30]
Median length of opioid therapy in days	14	IQR [11, 23]
Mean Finnegan score 24 hr prior to initiation of methadone therapy	10.8	SD (1.6)
Mean peak Finnegan score	15.6	SD (3)
Mean time to capture in days	1.4	SD (0.6)
Patients who received standard treatment (Scheme 1)	12	60%
Patients who received standard treatment (Scheme 1, no adjunct)	6	30%
Patients who needed escalated dose (Scheme 2)	8	40%
Patients who failed to progress through protocol (Backslid one or more steps)	10	50%
Patients who needed adjunctive therapy	11	55%
Readmission within 30 days of discharge	0	0

Abbreviations: IQR (interquartile range), SD (standard deviation)